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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,041	03/14/2000	Daniel R. Soppet	PF178D2	8342

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EXAMINER	
HUNT, JENNIFER ELIZABETH	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/525,041	SOPPET ET AL.	
	Examiner	Art Unit	
	Jennifer E Hunt	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-17 and 21-124* is/are pending in the application.

4a) Of the above claim(s) *1,9-17,38-45,64-71,90-97 and 116-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-37,46-63,72-89,98-115 and 124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 21-37, 46-63, 72-89, 98-115, and 124 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that there is no undue search burden. This is not found persuasive because as set forth in the original restriction requirement, the searches are not coextensive, and the search for one group would be insufficient for the other.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1, 9-17, and 21-124 are pending in the application. Claims 1, 9-17, 38-45, 64-71, 90-97, and 116-123 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 21-37, 46-63, 72-89, 98-115, and 124 are under consideration and addressed herein.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-37, 46-63, 72-89, 98-115, and 124 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are drawn to an antibody or portion thereof which binds to SEQ ID NO:2 and fragments thereof, and to an antibody or portion thereof which binds to the protein encoded by the cDNA contained in ATCC deposit #97129, and fragments thereof.

The specification discloses the isolation of a "colon specific gene" (SEQ ID NO:1), from a "colon cancer cDNA library". The colon specific gene contains an open reading frame which encodes a 158 amino acid "colon specific protein" which has been deduced from the isolated gene (page 6, lines 1-4). The specification discloses at page 11 that "while the colon specific gene are found in all cells of the body, their transcription to mRNA, cDNA, and expression products is primarily limited to the colon in non-diseased individuals," thus concluding that colon cancer metastasis might be detected by measuring increased levels of colon specific gene transcription products in "other tissues", an increase in such being indicative of colon cells which have metastasized to that "other tissue." The specification later states that the "colon specific gene" is overexpressed in colon cancer" (page 33, lines 7-8). The specification asserts that the instantly claimed antibodies are useful for detection of

colon cancer by detecting the colon specific gene polypeptide produced by the colon cancer specific gene (pages 14-16), as an anti-colon cancer targeting agent, or as an in vivo imaging agent.

There is no guidance or objective evidence that the instantly claimed antibodies would be useful, because it is not clear that the colon specific protein to which the claimed antibody binds, is expressed in colon cancer cells over normal colon cells and normal non-colon cells, at a level sufficient to produce any therapeutic or diagnostic utility. The limited teachings in the specification disclose only that the colon specific gene is present in all tissues, but transcription to mRNA, cDNA, and expression products is primarily limited to the colon in non-diseased individuals. The specification provides no guidance or objective evidence that the protein which to which the instantly claimed antibodies bind is ever expressed, nor is there any guidance or objective evidence that if such a protein were expressed, that it would be expressed at sufficient levels in colon cancer over normal colon tissue and normal non-colon tissues that it would be useful in diagnosis and treatment of colon cancer. It is noted that detection of a gene, or even cDNA or mRNA as diagnostic of a particular condition does not correlate to diagnosis by detection of the corresponding protein.

Those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is

blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Therefore, one of skill in the art would not be able to predict if SEQ ID NO:1 is in fact translated into the polypeptide of SEQ ID NO:2. The teachings in the specification are an invitation to experiment wherein the artisan is invited to elaborate a functional use for a putative polypeptide. Thus, predictability of protein translation is not necessarily contingent on its expression due to the multitude of homeostatic factors affecting transcription and translation. Moreover, the lack of

predictability of whether or not a protein is translated, is exacerbated when the protein function is unknown.

Further, with regard to use of the antibodies in a diagnostic or therapeutic method, the specification does not discuss or disclose levels of "colon specific gene" or transcription products thereof in colon cancer tissue, in normal colon tissue, or in normal non-colon tissue. No comparison is made between levels of colon specific gene transcription products in colon cancer tissue, in normal colon tissue, or in normal non-colon tissue. No colon specific protein is detected in colon cancer tissue, in normal colon tissue, or in normal non-colon tissue. Further, no function, structure, or qualities of the colon specific protein are set forth.

Therefore one of ordinary skill in the art at the time of applicant's invention would not have been enabled to use the instantly claimed antibodies and antibody fragments because there is no guidance or objective evidence that the colon specific protein bound by the instantly claimed antibodies is expressed, and further, if it is overexpressed in colon cancer cells and tissues over normal colon cancer tissues and normal non-colon tissues sufficient to be useful for any diagnostic or therapeutic use.

It is further noted that should applicant provide evidence that the colon specific protein is expressed, and that antibodies which bind to a colon specific protein might function for diagnosis or treatment of colon cancer, that the claims are not enabled for the broadly claimed antibodies. The claims encompass antibodies which bind minimally to fragments, or portions of the disclosed sequences, and thus encompass antibodies which bind to a broad range of polypeptides, including

fragments and variants of SEQ ID NO:2. It is known in the art that amino acid substitutions have significant impact on a protein's structure, which would impact the binding and activity of an antibody which binds to that protein. Thus the antibodies as claimed encompass a broad range of antibodies which would bind to a highly variant group of proteins and which would therefore induce highly different therapeutic and diagnostic effects.

Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of

heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3).

Therefore, due to the lack of guidance in the specification, the complex nature of the art, the lack of working examples, the unpredictability of the art, and the breadth of the claims detailed above, one of skill in the art at the time of applicant's invention would not be enabled to practice the full scope of the invention as claimed.

5. Claims 21, 23-37, 46, 48-50, 73, 75-89, 98, and 100-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are broadly drawn to an antibody which binds to a polypeptide of any size comprising a sequence that minimally contains portions of SEQ ID NO: 2, or the protein encoded by the cDNA contained in ATCC deposit #97129. The claims are drawn to a peptide of any size which is only defined by a small number of amino acid resides, hence the claims are drawn to an antibody which binds to amino acid residues which minimally contain only portions of SEQ ID NO:2 or portions of the protein encoded by the cDNA contained in ATCC deposit #97129. Thus the claims are drawn to a large genus of molecules. In the case of small identified amino acid residues claimed with open language, the genus of the polypeptides comprising a partial sequence encompasses a variety of subgenera with widely varying attributes. The specification discloses only the structural features of one species, the polypeptide of SEQ ID NO: 2. The specification lacks information to lead one of ordinary skill in the art to understand that the applicant had possession of the broadly claimed genus of antibodies at the time the instant application was filed. Applicant is referred to the guidelines for 112, first paragraph, published in the Official gazette and also available on www.uspto.gov.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner
Art Unit 1642

jeh
February 27, 2002

Sheela Huff
SHEELA HUFF
PRIMARY EXAMINER